Original article

Diagnostic utility of bone marrow sampling in HIV positive patients

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Objective: To evaluate the diagnostic utility of bone marrow (BM) sampling in HIV positive patients.
Design: Retrospective cohort analysis.
Setting: Specialist HIV/AIDS service in London.
Subjects: 215 consecutive HIV infected patients undergoing 246 BM samplings for investigation of pyrexia without localising signs, haematological abnormalities, or staging/investigation of lymphoma.
Main outcome measure: Diagnostic yield from (and impact on management of) BM sampling.
Results: Of 122 BM samples taken to investigate pyrexia, 33 (27%) revealed the cause on microscopy: unexpected lymphoma in seven (6%), mycobacteriosis in 25 (20%), and toxoplasmosis in one (1%). Marrow infiltration was confirmed in 11 of 38 BM samples taken for staging/investigation of lymphoma/leukaemia. In afebrile patients, of 22 with pancytopenia, BM samples showed HIV associated changes in 17 and specific diagnoses in five (mycobacterial infection in three, haemophagocytic syndrome in one, and megaloblastic change due to vitamin B-12 deficiency in one); of 21 with isolated thrombocytopenia, 20 (95%) BM samples showed immune thrombocytopenic purpura to be the cause and the remaining patient had BM changes of aplasia; of 29 with isolated anaemia, 28 had BM changes of HIV associated dysplasia/erythroid dysplasia and one had unsuspected iron deficiency; all 10 with isolated leucopenia/neutropenia had BM changes ascribed to HIV infection exacerbated by concurrent sepsis or medication; of four BM samples taken for other reasons, one showed mycobacterial infection.
Conclusions: BM sampling has diagnostic utility in HIV infected patients with pyrexia without localising signs, pancytopenia, and staging/investigation of lymphoma; this test has little value in the investigation of afebrile patients with isolated thrombocytopenia, anaemia, or leucopenia as HIV is usually the underlying cause.
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Keywords: haematology; bone marrow; HIV; mycobacteria; pyrexia

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Management protocols for HIV infected patients have often evolved from practices that were found to be useful for other patient groups. This is probably true for bone marrow sampling, although over the past few years there has been increasing evidence to support the value of this investigation for HIV infected patients, in particular for those who also have fever, haematological malignancy, and thrombocytopenia.[1–8] There are, however, few reports that examine the diagnostic utility of bone marrow (BM) sampling in unselected populations of HIV positive patients and the few studies that are published involve relatively small numbers of patient.[4 9 10] We have therefore reviewed BM samples taken from HIV infected patients over a period of nine years in order to provide an overall assessment of the diagnostic value of this investigation.

Methods

The study was performed in a central London unit specialising in the management of HIV, with a caseload that is largely made up of homosexual men with a small minority of patients from risk groups other than haemophilia. HIV infected patients who had undergone BM sampling between 1987 and 1995 were identified. From their case records, discharge summaries, and computer records, information was collected on patient characteristics, clinical indications for performing the marrow sample, results of microscopic examination of the marrow and other concurrent investigations, final diagnosis, and the value of the marrow sample in achieving a diagnosis.

All marrow aspirates were stained routinely with Giemsa and May–Grunwald and trephine samples with haematoxylin and eosin, reticulin, Giemsa, Ziehl–Neelsen and other special stains as appropriate.

Marrow aspirates were routinely cultured for bacteria using the Bactec system (Becton-Dickinson) and for mycobacteria with a biphasic medium.[11]

STATISTICS

The following tests for strength of associations were used with the help of the SPSS statistical package: continuous variables, t test; CD4 count, Mann–Whitney U test after logarithmic transformation; frequency of discontinuous variables, χ^2 test; independence of associations, multiple logistic regression analysis.

Table 1 Findings on microscopy of marrow samples taken to investigate pyrexia without localising signs

	No of marrow aspirates (%)	No of marrow trephines (%)	Combined aspirate and trephine (%)*
Non-Hodgkin's lymphoma	3 (2·5)	2 (2)	4 (3)
Hodgkin's lymphoma	1 (1)	2 (2)	2 (2)
Histiocytic lymphoma	1 (1)	0	1 (1)
Mycobacteriosis†	0	25 (23)	25 (20)‡
Toxoplasmosis	0	1 (1)	1 (1)
HIV changes only	108 (89)	79 (72)	89 (73)
Inadequate sample	8 (7)	1 (1)	0
Total	121 (100)	110 (100)	122 (100)

*Some lymphomas were found on both aspirate and trephine.
†The marrows showed granulomata and/or intracellular acid fast bacilli.
‡13 *Mycobacterium avium/intracellulare* (MAC) complex, two *M kansasii*, one *M chelonae*, one mixed MAC/*M simiae*, three *M tuberculosis*, five not typed.

Results

In all, 246 marrow samples were taken from 204 men and 11 women. Of these samples, 211 were taken by both trephine and aspirate, 33 were aspirate samples only, and two were trephine samples only. Ten (4%) of the marrow sampling episodes were retrospectively thought to have been performed without appropriate non-invasive investigations before the marrow test, and in 11 (4·5%) further episodes there was not enough information to judge. Apart from localised discomfort, no serious adverse effects due to marrow sampling were recorded. The results and value of the marrow samples were assessed in groups according to the clinical indication for performing the investigation.

PYREXIA WITHOUT LOCALISING SIGNS

Some 122 BM samples were taken from 106 men and five women. Results of marrow microscopy are given in table 1. A total of 33 (27%) new diagnoses were made to account for the pyrexia. The differences between patients with and without new diagnoses made on marrow microscopy were assessed for patient characteristics and concurrent laboratory tests. The most significant differences between the groups are shown in table 2. The CD4 count was not available for 36 (30%) patients as this test was not routinely available at this centre until 1992. On multivariate analysis, recent fall in any haematological variable was the only significant factor when this was included with CD4 count, age, and haemoglobin. When CD4 count was excluded from the model, age and haemoglobin became significant. There were no differences between the groups for total white cell count, platelet count, duration of pyrexia, ethnic origin, stage of HIV disease, sex, or route of acquisition of HIV. However, as only five patients were women, 11 had acquired infection by routes other than sex between men, and 19 were from ethnic groups other than white northern European, the numbers were too small to detect differences for these three characteristics. In 10 (30%) of the patients with new diagnoses from marrow microscopy (five lymphomas, four mycobacterial infection, and one toxoplasmosis), this was the only positive diagnostic test.

Eighteen of the 25 (72%) patients with mycobacteriosis diagnosed by marrow histological investigation were confirmed by positive cultures from marrow (15 positive), blood (11 positive), or sputum (two positive) a mean of 25 (range 8–60) days later, and a further three had mycobacteria on microscopical examination of other specimens but were culture negative on all specimens. In four (16%) patients, marrow histology was the only positive diagnostic test for mycobacteriosis but all four responded clinically to antimycobacterial therapy. Of the patients with negative marrow histology, 12 were subsequently shown to have atypical mycobacteriosis and two had tuberculosis on culture of blood (12 positive), marrow (eight positive), and/or other specimens (four positive). The sensitivity of marrow histology was therefore 22/34 (65%) for atypical mycobacteriosis and 3/5 (60%) for tuberculosis. Patients with mycobacterial infection diagnosed on microscopy were routinely started on an antibiotic regimen suitable for both tuberculosis and atypical mycobacteriosis, usually rifampicin and ethambutol with a third drug such as clarithromycin, until speciation was confirmed by culture when more specific treatment was instituted. When tuberculosis was the most likely diagnosis, such as in patients from ethnic minorities, initial treatment was with standard triple or quadruple antituberculosis drugs.

HAEMATOLOGICAL MALIGNANCY

Thirty eight bone marrow samples were taken from 33 men and two women. Two samples were from patients with primary central nervous system (CNS) lymphoma; both were negative. Four samples were taken to assess relapse or treatment response; three were positive for malignant cells (one non-Hodgkin's lymphoma (NHL), one chronic granulocytic leukaemia, and one Hodgkin's lymphoma) and one was negative (NHL). The results from marrow samples taken for disease staging are shown in table 3. Of the eight positive staging samples, three were positive on aspirate only and two on trephine only. Four of the patients who had marrow sampling for staging purposes were already known to have stage 4 lymphoma and one of these had marrow involvement. It was felt that marrow sampling was appropriate in all cases, even in those who would receive chemotherapy anyway, as the knowledge of marrow involvement allowed more accurate assessment of treatment response.

Table 2 Pyrexia without localising signs: differences between patients with and without a positive diagnosis made on marrow microscopy

Variable	Patients with: Negative marrow	Positive marrow	p Value
Mean (SD) age (years)	36·6 (8·1)	33·3 (6·2)	0·03
Mean (SD) haemoglobin (g/l)	10·1 (2·1)	8·8 (2·4)	0·01
Recent fall in any haematological variable (No of patients (%))*	27 (31)	18 (54)	0·02
Median (range) CD4 count (× 10⁶/l)	60 (0–430)	20 (0–320)	0·07

*Defined as a fall in any one or combination of haemoglobin (by > 20%), platelet (by > 30%), or total white cell (by > 30%) count in the preceding two months.

Table 3 Lymphoma involvement of marrow samples taken for clinical staging

Type of lymphoma	*Marrow aspirates (+ve/total) (%)*	*Marrow trephines (+ve/total) (%)*	*Combined aspirates and trephines (+ve/total) (%)*
Non-Hodgkin's	4/29 (14)	2/27 (7)	5/29 (17)
Hodgkin's	0/1	1/1 (100)	1/1 (100)
Histiocytic	1/1 (100)	0/1	1/1 (100)
T cell lymphoma/leukaemia	1/1 (100)	1/1 (100)	1/1 (100)
Overall	6/32 (19)	4/30 (13)	8/32 (25)

CYTOPENIAS IN AFEBRILE PATIENTS

Pancytopenia

Twenty two bone marrow samples were taken from 21 men and one woman. All had late stage disease (median CD4 count 20 × 10^6/l (range 0–150 × 10^6/l) (normal range 350–2200 × 10^6/l)). Of the 22 aspirates, 17 showed varying degrees of HIV related dysplasia, one HIV related haemophagocytic syndrome, one megaloblastic change due to vitamin B-12 deficiency, and three were inadequate. Of 20 trephines, 15 showed HIV related dysplasia, three mycobacteriosis, one non-specific granulomas, and one was inadequate. Combining the results of the aspirates and trephines, 5/22 (23%) new diagnoses were made (three mycobacteriosis, one megaloblastic change due to vitamin B-12 deficiency, one HIV related haemophagocytic syndrome). The remaining 17 cases were considered to be due to HIV related marrow dysplasia exacerbated by concurrent medication, sepsis, or hypersplenism. No patient characteristics or laboratory markers correlated with specific diagnoses.

Thrombocytopenia

Twenty one BM samples were taken from 20 men and one woman; 21 had aspirates and 14 also had trephine samples. The median platelet count was 19 (range 9–49) × 10^9/l and the median CD4 count was 130 (range 40–780) × 10^6/l. All except one of the aspirates and trephines showed normal or increased megakaryocyte numbers with varying degrees of associated marrow dysplasia consistent with HIV related immune thrombocytopenic purpura (ITP). The one exception showed marked hypoplasia of all cell lines.

Anaemia

Twenty nine BM samples (29 aspirates and 21 trephines) were taken from 27 men and one woman. The mean haemoglobin (SD) was 76 (13) g/l and the median CD4 count was 30 (range 10–340) × 10^6/l. Apart from HIV related dysplasia and erythroid hypoplasia seen to varying degrees in most marrow samples, the only other significant change was diminished iron stores in one sample from a patient whose peripheral blood samples had not shown iron deficiency. The anaemia was felt in the majority to be due to HIV related marrow dysplasia exacerbated in some cases by concurrent medication except for the one case of iron deficiency.

Leucopenia/neutropenia

Ten BM samples were taken, all from men. No additional diagnoses were made other than HIV related marrow dysplasia. Medication or acute sepsis was thought to have contributed to the low white cell count in three cases.

OTHER INDICATIONS

Four BM samples, all from men, were taken for the investigation of suspected lymphoma in two, suspected histoplasmosis in one, and cachexia in one. Three showed HIV changes only but one of the two taken for suspected lymphoma showed mycobacterial infection.

Discussion

The value of these data lies in the fact that they allow us to define more clearly when a BM sample will be of use in the investigation of illness in HIV positive patients. It shows that BM sampling is clearly of benefit in the investigation of selected patients with pyrexia in whom a cause was found immediately in 27%. Some 6% of such patients had previously undiagnosed lymphoma and 20% were shown to have a mycobacterial infection which was diagnosed an average of 25 days earlier than with concurrent culture. This ability to make an early diagnosis has obvious advantages with respect to prompt treatment and avoidance of other unnecessary investigations.

Previous studies have shown that marrow culture increases the diagnostic yield for mycobacterial infection in HIV infected patients,[1-3 10 12-15] although the reported sensitivity of microscopic examination has varied from 25% to 85%.[1 2 10 13-15] In this study, where Ziehl–Neelsen staining was used, the sensitivity of microscopy was 65%. Experience elsewhere suggests that sensitivity may be further increased if auramine–rhodamine or Romanowsky stains are used.[13 15] Some authors have suggested that microscopy of liver biopsy material may be more sensitive for the diagnosis of disseminated mycobacterial infection,[2] but this method would miss those patients with BM infiltration by lymphoma who present with fever. In addition, it has been reported that diagnostic liver biopsy carries a significant burden of morbidity and mortality in HIV infected patients.[16] As with other studies, we found that marrow microscopy detected a significant proportion of both disseminated atypical mycobacteriosis and extrapulmonary tuberculosis.[1-3 10 13-15]

Anaemia has been previously recognised to be more common in patients with mycobacterial infection,[17] as has a low CD4 count.[3] We also found a significant association between mycobacterial infection of the marrow and anaemia or other features of marrow dysfunction, although these associations did not apply to every patient. It is likely that the CD4 count would have also been a significant correlate with a positive outcome on marrow sampling for fever if more data had been available. However, there is considerable overlap between the groups of patients with and without diagnostically helpful marrows with regard to the four variables in table 2 and it unlikely that they will be of use prospectively in selecting patients for BM sampling. Marrow

microscopy has the additional advantage of aiding the diagnosis of disseminated toxoplasmosis, as our study showed, and also other infections such as leishmaniasis and disseminated fungal infections including those caused by *Histoplasma capsulatum* and *Penicillium marneffei*.[3 18 19]

Most studies on BM sampling for HIV related pyrexia of undetermined origin recognise its value in diagnosing opportunistic infection,[1-3 10] but few recognise its use in identifying lymphoma as the cause of pyrexia where it is usually of the Hodgkin's type.[20] The large sample size in our study has enabled us to show that a proportion of the cases of pyrexia without localising signs may be due to lymphoma of all types (6%). However, this relatively high proportion may also be a function of referral patterns, stage of disease, or other selection biases.

Much has been written on the marrow changes caused by HIV and some studies have correlated these changes with haematological indices in peripheral blood.[4 21] Little has been documented on the value of marrow sampling as a diagnostic aid to the cause of cytopenias other than thrombocytopenia.[7 8] This study is, therefore, useful in that it clearly demonstrates in our patient group that marrow sampling is of little diagnostic value in afebrile patients with solitary anaemia or leucopenia. Once marrow suppressive drugs had been stopped in patients with either type of cytopenia and investigations performed for iron and vitamin deficiency and parvovirus infection in anaemic patients,[22 23] the cause was HIV related marrow dysplasia, sometimes associated with concurrent acute sepsis or metabolic disease. The same may be said of thrombocytopenic patients. Once drugs and acute sepsis were excluded, the majority (95%) of patients were found to have normal or increased megakaryocytes in the marrow consistent with HIV related ITP. There is, therefore, a valid argument that all such patients should be empirically treated for ITP with agents such as zidovudine, glucocorticoids, or immunoglobulin, and a marrow aspirate alone performed in only those patients who fail to respond to treatment.

Pancytopenia in afebrile patients in our study was found to be a significant indicator of disease other than marrow dysplasia, with 23% of marrows revealing additional diagnoses. These patients were selected in the sense that most of them had been previously tested for vitamin B-12 and folate deficiency, marrow suppressive drugs had been stopped, and all had CD4 counts of less than 150 $\times$ 10^6/l. Perhaps the most interesting feature, as all were afebrile, was the finding of mycobacterial infection in three of the five patients with new diagnoses. HIV related haemophagocytic syndrome, which we found in one patient, is a well known cause of pancytopenia.[24]

Except for primary CNS lymphoma, it is well recognised that there is a significant rate of marrow involvement in HIV associated lymphomas, and the overall rate of 25% found in this study accords with others.[4-6] We had only a few cases of Hodgkin's lymphoma but larger studies have also shown that marrow involvement is more common than in lymphomas of the non-Hodgkin's type.[4-6 25] The identification of such patients is important as it allows the planning of treatment, positive samples automatically indicating that cytotoxic drugs will be needed.[26]

Using these data we can therefore draw up clinical guidelines to indicate when marrow sampling will and will not be useful, with the proviso that these guidelines will be most helpful in populations that are composed of patients who are similar to ours (table 4). Knowing that marrow sampling is unlikely to give a new diagnosis in most cases of cytopenia, physicians can be confident that once drug effects, infection, and vitamin deficiencies have been excluded, the cause is usually HIV, and therapeutic strategies aimed at supporting marrow function and inhibiting HIV replication are most likely to be effective for these problems.

Table 4 Guidelines to aid the decision as to when marrow sampling may be useful in HIV positive patients

Marrow aspirate and trephine sampling is likely to be helpful in the following circumstances:

Pyrexia without localising signs
- In the ambulant outpatient who is not distressed by the fever, perform marrow sampling after four weeks have elapsed (to allow time for mycobacteria to grow in culture) following initial investigations which should include three blood cultures for bacteria and mycobacteria and appropriate culture of other samples. Appropriate imaging and tissue sampling should also have been performed according to the patient's history and the finding of any focal physical signs.
- In the acutely ill patient or patient who is awaiting cytotoxic therapy, perform marrow sampling after one week's inpatient stay if the cause of the fever is not revealed by investigations and possible empirical therapy for acute bacterial infection and other common causes of fever (such as cryptococcal and *Pneumocystis carinii* infection) have been excluded.

*Pancytopenia**
- After non-essential potentially marrow suppressive drugs have been stopped and vitamin B-12 and folate levels measured.

Staging of lymphoma
- If the patients is a suitable candidate for cytotoxic chemotherapy.

Marrow aspirate only may be helpful for:

*Thrombocytopenia**
- After potentially marrow suppressive drugs have been stopped, any acute bacterial sepsis treated and if the patient fails to respond to a therapeutic trial of glucocorticoids, immune globulin, or zidovudine.

Marrow sampling will only rarely be helpful for:

*Anaemia**
- After investigation for iron, vitamin B-12, and folate deficiencies and the exclusion of parvovirus infection and the effects of drugs, acute bacterial sepsis, or severe metabolic disease such as renal failure or haemolytic uraemic syndrome.

*Leucopenia or neutropenia**
- After cessation of marrow suppressive drugs (for example, ganciclovir) and the exclusion of acute bacterial sepsis.

*In afebrile patients only, otherwise follow the guidelines for fever without localising signs.

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A cobblestone

Prison doctors beware!

Penile skin nodules are not uncommon. Genitourinary physicians are familiar with the various conditions that present as nodular penile lesions. Genital scabies, often present as nodules and lymphoceles on the shaft of the penis, may harden in time to form nodular lesions (sclerosing lymphangitis). In Peyronie's disease, painless, fibrous nodules can be felt on the shaft. Solitary warts and keloids on the coronal sulcus can sometimes be felt as nodules under the overlying foreskin. In men with poor penile hygiene, accumulation of smegma over a long period of time can eventually harden and produce nodules under the foreskin. Sebaceous cysts and retention cysts of the skin of the penis are among the other causes of penile nodules. Rare causes of multiple penile nodules include Bowenoid papulosis and the pruritic papules often seen in HIV infected patients. The nodular form of lichen planus of the penis is less frequently encountered.

An unusual form of penile nodule is described here. A 26 year old white male prison inmate was referred with a long standing history of episodic penile discomfort culminating in a sense of swelling and tightness at the bulb of the penis. Earlier screening for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* from the urethra had given negative results. Serological tests for syphilis, VDRL, and TPHA were also negative.

On examination, he appeared well built and healthy, prone to be garrulous, and throughout the interview smoked a rolled up cigarette with the unmistakable pungency of cannabis. On examination, there were no skin blemishes or lymphadenopathy. The eyes, mouth, and throat appeared normal. Genital examination showed normal scrotum and contents. The uncircumcised penis appeared normal over the shaft, but over the coronal sulcus on the dorsal surface a nodule the size of a pea was apparent. On palpation this felt firm, freely mobile, and non-tender. To examine the lesion in more detail, the patient was asked to retract the prepuce. Surprisingly, he was reluctant to do this and needed some coaxing before agreeing, commenting that he "should not be showing this". When the foreskin was pulled back, out popped the penile nodule on to the floor! This, on inspection, proved to be a lump of cannabis resin wrapped firmly in a tissue and was of a size that fitted snugly in the coronal sulcus.

There is no previous report in the literature of a penile nodule resulting from the use of this particular anatomical crevice as a place for secretion of proscribed items.

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